

Cleveland Clinic Quarterly

A Bulletin Published by
The Staff of the Cleveland Clinic
CLEVELAND, OHIO

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Vol. 9

JULY, 1942

No. 3

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CLEVELAND CLINIC QUARTERLY

Issued in four numbers during the year; one in January, one in April, one in July and one in October, by Cleveland Clinic Foundation, 2020 East 93rd Street, Cleveland, Ohio.

Entered as second-class matter March 4, 1935, at the Post Office
at Cleveland, Ohio, under the Act of August 24, 1912.

ATYPICAL PAIN IN ANGINA PECTORIS

W. L. PROUDFIT, M. D. and A. CARLTON ERNSTENE, M. D.

In its typical form the syndrome of angina pectoris seldom offers difficulty in diagnosis. The pain or discomfort is situated in the substernal region, is precipitated by exertion, may or may not radiate from its site of origin, and is relieved promptly by rest and nitroglycerine. Atypical forms of the syndrome, however, are not so well recognized and often are responsible for erroneous diagnoses. It is the purpose of the present report to emphasize the frequency with which the pain of angina pectoris arises in regions other than the substernal area and to point out the more common of the atypical sites of origin.

MATERIAL AND RESULTS

Five hundred cases of angina pectoris due to coronary artery disease were analyzed. The cases constituted a consecutive series except for the fact that a few records were excluded because of insufficient information in the clinical history or because no electrocardiogram had been made.

In the entire series of 500 cases there were 378 instances in which the pain or discomfort originated in the substernal region and 122 in which it arose in some other area. The pain, therefore, was atypical in its site of origin in 24.4 per cent of the patients. The ages of the patients, distribution according to sex, and the incidence of arterial hypertension are shown in Tables 1 and 2. None of these factors appeared to be of significance in relation to the occurrence of atypical pain. The initial location of the pain in the atypical cases is presented in Table 3. The pain originated in the precordial area in 34 cases, an incidence of but 6.8 per cent of the entire series of 500 cases. Pain originating in the extremities occurred with practically the same frequency as precordial

TABLE 1
Age Distribution in Typical and Atypical Angina Pectoris

Age Group	Typical (378 cases)	Atypical (122 cases)
	No. of Cases and Percentage	No. of Cases and Percentage
30-39	9 (2.4%)	3 (2.5%)
40-49	80 (21.2%)	30 (24.6%)
50-59	132 (34.9%)	52 (42.6%)
60-69	123 (32.5%)	31 (25.4%)
70-79	31 (8.2%)	5 (4.1%)
80 and over	3 (0.8%)	1 (0.8%)

TABLE 2

Sex and Blood Pressure in Typical and Atypical Angina Pectoris

Blood Pressure	Typical (378 cases)		Atypical (122 cases)	
	No. of Cases and Percentage		No. of Cases and Percentage	
	(Male)	(Female)	(Male)	(Female)
Normal.....	158 (41.8%)	22 (5.8%)	54 (44.3%)	10 (8.2%)
Elevated*.....	123 (32.5%)	75 (19.8%)	44 (36.1%)	14 (11.5%)

*In this study a blood pressure which was over 150/90 mm. of mercury was considered to be elevated.

pain, while discomfort arising in the abdomen was somewhat less common. Less common still were those cases in which the initial location of the distress was the neck, throat, jaws, or upper back.

The data presented in Table 3 also indicate that there are two principal varieties of atypical pain in angina pectoris, namely, a form in which there is no radiation to the substernal area and one in which the discomfort spreads from its site of origin to involve the substernal

TABLE 3

Location and Radiation of Pain in Atypical Angina Pectoris

Initial Location	No. of Cases	Percentage of Entire Series (500 cases)	Radiation to the Substernum
Chest.....	38	7.6%	
Precordium.....	34	6.8%	
Other than precordium.....	4	0.8%	
Upper extremities...	35	7.0%	19 (54.3%)
Left.....	17	3.4%	9 (53.0%)
Right.....	3	0.6%	2 (66.7%)
Both.....	15	3.0%	8 (53.3%)
Epigastrium.....	29	5.8%	13 (44.8%)
Neck, throat, and jaws.....	13	2.6%	1 (7.7%)
Back.....	7	1.4%	3 (42.9%)

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region. The latter form constitutes the so-called angine renversée of Potain. In addition to these two types, a third variety of atypical pain was encountered in which the distress was predominantly peripheral in location but was accompanied by slight substernal discomfort. In the present series there were 81 cases in which the pain did not radiate to the substernal region, 36 in which radiation to the substernal area occurred, and 5 in which the peripheral pain was accompanied by slight substernal discomfort. In several of the cases belonging to the first of these groups there had been one or more attacks in which the pain had originated in, or had radiated to, the substernal region, but distress of this kind was not a part of the patient's usual attacks. In a few cases in the first and second groups also there originally had been one or more attacks in which the pain arose in the substernal region and the attacks later had assumed their atypical character. In each of the five cases in the third group, the history of substernal discomfort was obtained only by direct questioning, and the distress never amounted to more than a distinctly minor feature.

Eleven (9 per cent) of the patients who had atypical pain and 61 (16 per cent) of those who had typical pain had experienced myocardial infarction before they were first seen. Electrocardiographic abnormalities were recorded in all but a few of the atypical cases, and the heart was enlarged on roentgenologic examination in 30 of the 122 patients. Nitrite therapy for the attacks had been employed at some time in 34 of the atypical cases and had given relief in all but one patient.

DISCUSSION

It is generally accepted¹ that cardiac stimuli which result in the pain of angina pectoris are transmitted from the heart entirely by way of sympathetic afferent fibers. A few of these fibers pass directly from the heart to the upper four or five thoracic sympathetic ganglia, but the great majority reach these ganglia by way of the middle and inferior cardiac nerves and the corresponding cervical ganglia. All of the fibers pass through the sympathetic ganglia without interruption and reach their ganglion cells in the upper four or five thoracic posterior nerve root ganglia by way of the white rami communicantes. The central processes of the ganglion cells form synapses with sensory cells in the gray matter of the posterior horns of the spinal cord, and from this point two possible routes exist. The first of these is known as the direct pathway, and over it stimuli are transmitted directly to the thalamus. Apparently it is this type of stimulation that results in the sensation of pain in the substernal region. The second route is known as the indirect

pathway and is the one that is responsible for the radiation or referred pain of angina pectoris. This pathway results from the fact that certain of the sympathetic cardio sensory nerves form synapses with posterior horn cells that also serve somatic afferent nerves. The irritability of these cells is increased by the stimuli arriving over the cardio sensory nerves so that somatic impulses produced by the ordinary contacts with the outside world cause the central neurone to discharge (theory of summation of impulses). The pain is referred to the areas from which the somatic impulses arise. Spillane and White² believe that the theory of referred pain explains the ordinary extrathoracic pain of cardiac origin but does not account for the type of pain which begins peripherally and spreads toward the thorax. They are of the opinion that the latter pain is the result of an autonomic reflex which causes painful peripheral spasm of smooth muscle.

Although many observers have directed attention to the occurrence of atypical pain in angina pectoris, few studies have been made to ascertain its frequency and most common varieties. Riseman and Brown³ reported that in 26 of 100 cases of angina pectoris, the pain originated in an area other than the substernal region. In these cases the most common sites of origin were the cardiac apex or other areas of the anterior chest, thoracic spine, epigastrium, and left arm. Bourne and Scott⁴ recorded pain of atypical origin in approximately 30 per cent of 112 cases of angina pectoris, the most common of the atypical sites being the left chest, right chest, and epigastrium. In the present study the incidence of atypical pain was 24 per cent, and the most common sites of origin of the pain in the atypical cases were the precordium or other areas of the anterior chest, the upper extremities, epigastrium, and the neck, throat, or jaws.

Fortunately, a detailed clinical history almost always enables one to make a correct diagnosis of angina pectoris even in those cases in which the pain is not typical in its origin. The attacks are precipitated by exertion or excitement and are particularly liable to occur while walking in cold weather or soon after eating. In both typical and atypical cases, the patient often experiences difficulty in describing the pain and frequently refers to it as a sensation of fulness, pressure, tightness, squeezing, or heaviness. Usually the distress is of such a nature as to enforce cessation of all activity and at times is accompanied by a sense of impending death. The pain may or may not radiate from its site of origin, but when it does do so the fact is of diagnostic importance. In cases in which the pain originates in an atypical area, there is often no radiation or accompanying sensation of distress in the substernal region. At times, however, the patient, on questioning, will acknowledge some

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minor substernal discomfort as a part of his usual attacks or will recall having had substernal pain during one or more unusually severe seizures. All symptoms are relieved by rest, usually within a few minutes. It is extremely unusual for the attack to last as long as fifteen minutes. Nitroglycerine and similar preparations almost invariably give prompt relief from the symptoms. Physical examination and electrocardiogram may or may not reveal evidence of organic heart disease. If the electrocardiogram is normal, a record made during an induced attack of pain frequently shows changes in the S-T segment or the T wave of greater degree than occur in the tracings of normal individuals after the same amount of exercise.⁵

It is of course of great importance that all cases of angina pectoris be correctly diagnosed in order that proper therapy may be instituted and the patient advised concerning his future mode of life. Measures of this kind can do much not only to increase the patient's comfort but also to prolong his life, while incorrect management, on the other hand, is very liable to increase the gravity of an already serious prognosis. In cases of atypical pain arising in the epigastrium, accurate recognition may even spare the patient the risk of an unnecessary operation.

SUMMARY AND CONCLUSIONS

Five hundred consecutive cases of angina pectoris due to coronary artery disease were analyzed in order to determine the frequency with which the pain originated in regions other than the substernal area. In 378 cases the pain arose in the substernal region, and in 122 (24.4 per cent) it originated in some other area. The most common of the atypical sites of origin were the precordium, upper extremities, epigastrium, and the neck, throat, or jaws. The age and sex of the patients and the presence of arterial hypertension were not of significance in relation to the occurrence of atypical pain.

There are two principal varieties of atypical pain in angina pectoris, namely, a form in which there is no radiation to the substernal area and one in which the discomfort spreads from its site of origin to involve the substernal region (*angine renversée*). A third and less common variety also was encountered in which the distress was predominantly peripheral in location but was accompanied by slight substernal discomfort.

The diagnostic criteria of angina pectoris have been reviewed, and the importance of accurate recognition of all cases of the syndrome has been emphasized.

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A REVIEW OF 938 GASTROSCOPIC EXAMINATIONS*

R. J. F. RENSHAW, M.D.

Modern gastroscopy was introduced in 1932 and was received with mixed enthusiasm and skepticism. Today gastroscopy is an accepted procedure, but it is in a period of re-evaluation. Some of the early enthusiastic claims for the method have been discarded, others modified, and others verified. Except for certain problems in clinical research, gastroscopy is being used chiefly for two diagnostic purposes: (1) to examine the stomach when the clinical and roentgenologic findings do not explain the clinical picture (either negative or indeterminate findings), and (2) to confirm the roentgenologic findings of a gastric ulcer or carcinoma. It has been well demonstrated that the combination of roentgenoscopy and gastroscopy is more accurate than either method alone. If both examiners are in agreement, the clinician may be reasonably certain that the diagnosis is correct. If, however, there is disagreement, further study and observation is indicated. In such instances of disagreement it will be found that on the first examination the roentgenologist will be correct in about 50 per cent of the cases and the gastroscopist correct in about 50 per cent.

We have recently reviewed our experience covering the last 938 consecutive gastroscopic examinations.¹ Our experience is in accord with the foregoing statements and also with Templeton and Boyer² who compared the roentgenologic and gastroscopic findings in carcinoma and its benign counterparts. We were able by operation or clinical observation to follow-up 170 patients adequately. (Table 1) In this group of 170 cases both the roentgenologic and gastroscopic diagnoses at the first examination were in agreement and were correct in 109 instances, or 64.2 per cent. In 15 cases, 8.8 per cent, the roentgenologist made the correct diagnosis while the gastroscopist was incorrect or indeterminate. If the examiner admitted some question about the diagnosis even though it subsequently proved to be correct, or if he admitted the possibility of a second or third diagnosis, such diagnoses were considered to be inconclusive and indeterminate. There were 23 cases, 13.5 per cent, in which the gastroscopist made the correct diagnosis while the roentgenologist was indeterminate or incorrect. In 9 instances, or 5.3 per cent, both the roentgenologist and gastroscopist were incorrect, and in 14 cases, 8.2 per cent, both were inconclusive or indeterminate.

*An abstract of a paper presented to the American Gastro-enterological Association, Atlantic City, June 8, 1942 and to be published in the American Journal of Digestive Diseases.

TABLE 1
COMPARISON OF FIRST ROENTGENOLOGIC
AND GASTROSCOPIC EXAMINATIONS

	Ulcer	Car- cinoma	Other Findings			
Concurring..... Diagnoses	9 (3)	18 (16)	82 (10)		109 (29)	64.2%
X-ray Correct..... Gastroscopic Incorrect or Indeterminate	9 (1)	4 (4)	2 (1)		15 (6)	8.8%
Gastroscopic Correct..... X-ray Incorrect or Indeterminate	5	7 (4)	11 (2)		23 (6)	13.5%
Both Incorrect.....	3 (3)	5 (5)	1		9 (8)	5.3%
Both Indeterminate.....				14	14	8.2%

Figures in parentheses indicate cases confirmed by operation or autopsy.

Obviously, one must consider certain qualifying factors in these figures, although the qualifying factors do not invalidate the results. One factor that should be emphasized is that not all the examinations were made by the same roentgenologist or roentgenologists of equal experience. Another factor is that cases of chronic gastritis were included in this comparison. The roentgenologists at the Clinic are of the opinion that they should rarely make a diagnosis of gastritis purely on the basis of the roentgenologic findings. They believe this to be in the field of the gastroscopist. If, then, this series were large enough to limit the comparison to only carcinoma and benign ulcer, no doubt the accuracy of the roentgen diagnosis would be markedly higher. However, the consideration of chronic gastritis was not omitted from this series because chronic gastritis is a definite clinical entity which at times produces disturbing or alarming symptoms and for which we must have some adequate means of diagnosis. At the present time gastroscopy is the only dependable clinical method for the diagnosis of chronic gastritis.

In reviewing these 938 examinations we were interested in determining the incidence of major or significant gastroscopic contributions, the failures, and the reasons for failures. This has been more fully covered elsewhere,¹ but it is of significance that the gastroscopist established the

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major diagnosis or added some significant unknown fact to the case that materially altered the treatment or prognosis in 25.6 per cent of all patients examined.

In 55 per cent of the cases examined gastroscopy made a minor contribution. A large part of these were confirmation of normal roentgenologic findings in persons suspected of having irritable colons. Whereas many of these patients formerly had gastroscopic examinations at the first consultation, we now recommend a trial on "bowel management" and if no improvement is noted, then a gastroscopic examination is indicated. Another large part of the 55 per cent was made up of patients with duodenal ulcer in whom gastritis was found. We now omit the routine gastroscopic examination in patients with duodenal ulcer unless some gastric complication is suspected. In light of our present knowledge the coexistence of gastritis with duodenal ulcer has not altered the prognosis or treatment. Perhaps the clinical research worker will in time prove the significance of gastritis and thereby prove the need for gastroscopy in these cases. Whereas gastroscopy was of major value in 25.6 per cent of the cases and of minor value in 55 per cent, there was but 19 per cent where the examination was incomplete or the diagnosis was indeterminate or wrong. The chief cause of unsatisfactory examinations was the gastroscopist's inability to visualize an area in question, for example, a prepyloric ulcer. Two points warrant emphasis regarding the gastroscopic failures. One is the personal equation factor that gastroscopy is a visual method dependent entirely upon the examiner's skill of interpretation. The second important point is the technical difficulties inherent in the method. There are certain constant blind areas and other inconstant blind areas. A portion of the instrument is flexible, and if angulated by anatomical structures beyond its useful range, no picture or an inadequate one is obtained. The stomach is in constant motion and what may be glimpsed at one moment may never be brought into the field again. The clinician asking for gastroscopic consultation should bear in mind these and other limitations of gastroscopy.

On the basis of our experience we believe *gastroscopy is indicated in four groups of patients:*

- (1) Those with negative roentgenologic examinations of the gastrointestinal tract in whom one still suspects gastrointestinal disease.
- (2) Those with indeterminate or inconsistent roentgenologic findings.
- (3) Those with gastric ulcer.
- (4) Those with carcinoma, except frank, near-terminal cases.

SUMMARY

A review of 938 consecutive gastroscopic examinations revealed:

1. That the gastroscopist made a significant and major diagnosis not revealed by other methods in 25.6 per cent of all cases examined.
2. That the gastroscopist added a confirmation or a new minor diagnosis in 55 per cent.
3. That the gastroscopic examination was unsatisfactory or indeterminate or incorrect in 19 per cent.
4. That the chief causes of the gastroscopist's failures were technical difficulties inherent in the method. Incorrect diagnoses were but a small percentage.
5. That the gastroscopist is no more likely to be correct or to err in diagnosis than his colleague, the roentgenologist. Using only the first examination for comparison both examiners were in agreement in 64.2 per cent of all cases. Both were wrong in 5.3 per cent, and both were indeterminate in 8.2 per cent. In 22.3 per cent one or the other was indeterminate or incorrect. This latter group was divided approximately equally between gastroscopist and roentgenologist.

A certain percentage of all gastrointestinal problems cannot be considered as having been properly and adequately studied unless a gastroscopic examination has been done, but the clinician must be aware of the fact that while gastroscopy may be of great value it has certain limitations.

We believe the indications as given are conservative and practical.

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TWO CASES OF DIABETES MELLITUS

One with Myxedema and one with Addison's Disease

E. PERRY McCULLAGH, M. D.

For a long time it has been recognized that glucose tolerance is increased in patients with hypothyroidism and that diabetes mellitus is aggravated by coexisting hyperthyroidism.^{1, 2} Attention also has been called to the fact that diabetes is more common in the presence of hyperthyroidism than in its absence.³ The mechanism by which hyperthyroidism produces diabetes-like metabolic changes appears to be as follows: The rate of oxidation of carbohydrates by the tissues of the body is increased. This results in a rapid flow of stored sugar from the liver into the blood stream tending to deplete the liver stores.⁴ Because the absorption rate of glucose from the intestine is accelerated, the postprandial rise of blood sugar is further exaggerated.⁵ Meanwhile, the liver is further depleted because of an increased rate of oxidation within its cells. Thus the whole picture rather closely simulates that found in diabetes mellitus. For the same reasons latent diabetes may manifest itself, and existing diabetes may become more severe in the presence of hyperthyroidism.

In myxedema the whole process is reversed. The ameliorating effect of thyroidectomy upon diabetes mellitus has been tested clinically⁶ and has not been found to be of practical therapeutic value. Cases of diabetes and myxedema thus present an unusual and interesting metabolic picture. They prove that thyroidectomy cannot be expected to have a curative effect on diabetes mellitus. Diabetes and myxedema have coexisted in five cases which have come under my supervision. One of these is reported here.

Case 1. The patient, a 62 year old white woman, had been well and active until three years prior to examination. Since that time she had noted a gradually increasing sense of fatigue and an increased need for sleep. Her face, eyelids, arms, hands, and ankles had become puffy, and her skin and hair were dry. Her memory was diminished. She became intolerant to cold, and her hands and feet were often numb. There was mild dyspnea on exertion. Repeated urinalyses had failed to show any evidence of kidney disease. Her weight had increased 15 pounds in the preceding year. Menopause had occurred at the age of 50 and had been accompanied by few symptoms.

Glycosuria had been discovered 12 years previously and had been observed occasionally since. No insulin had been used, and no dietary regimen had been followed for three years. She had never had the cardinal symptoms of diabetes nor any of the symptoms of common complications.

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One brother had died of pernicious anemia and one sister of diabetes. The patient had had two pregnancies, and her two normal children were living and well. She had had no surgical operations.

Physical examination. The patient's height was 65½ inches; weight 199½ pounds; temperature 98.4° F.; pulse 66; blood pressure 140 mm. systolic and 92 mm. diastolic. Her appearance was typical of myxedema. The face was puffy and sallow, and there were practically no eyebrows. The skin, especially on the face and backs of the hands, was dry and somewhat scaly. The subcutaneous tissues had a doughy feeling, and there were well marked supraclavicular pads. The relative cardiac dulness did not appear to exceed normal. The heart sounds were clear but distant. Occasional extrasystoles were present. There was crepitation and stiffness of the knees. The reflexes in the arms and legs were physiological, except that the patellar reflexes and the Achilles tendon reflexes were sluggish and exhibited a peculiar, slow recovery rate. There was a slight sensory impairment in both feet and lower legs to perception of heat, cold, touch, and sharp-dull differentiation. The dorsalis pedis pulse was not detected.

LABORATORY TESTS

Blood chemistry and serology revealed fasting blood sugars of 258 and 227 mg. per cent; urea 39 mg. per cent; cholesterol 272 mg. per cent; and CO₂ combining power 53.8 volumes per cent. Serum proteins totalled 7.3; albumin 5.0; and globulin 2.3 grams per cent.

Blood count disclosed 4,310,000 red blood cells; 5,500 white blood cells, with 54 per cent neutrophiles, 39 per cent lymphocytes, 1 per cent eosinophiles, 5 per cent monocytes, and 1 per cent basophiles; the volume of packed red blood cells was 87 per cent of normal, with an hematocrit level of 39 cc. per 100 cc.; volume index 1.01; hemoglobin 84 per cent of normal or 13 grams per 100 cc. (Haden-Hauser); color index 0.98; and icterus index 6.0.

Urinalyses revealed a specific gravity which varied from 1.018 to 1.026; a faint trace of albumin in some specimens; no sugar.

Urea clearance evidenced 65 and 60 per cent excretion in each of two hours.

Hippuric acid liver function test was 130 per cent of expected normal.

Basal metabolic rates were minus 29 per cent and minus 27 per cent.

The electrocardiogram showed changes commonly recognized as being due to myxedema: rate 76, sinus rhythm, slurring of the QRS complexes, T₂ iso-electric, T₃ inverted, left axis deviation, and ventricular premature beats. Parts of the electrocardiograms before and after nine months of treatment are shown. (Fig. 1) The second tracing shows a complete return to normal.

Course of the myxedema. Desiccated thyroid was prescribed at once in doses of 2 grains per day orally. The dosage was raised to 3 grains daily in a week and has been maintained there for 22 months to the present time. The basal metabolic rate rose to +6 per cent in a month, was ± 0 per cent in 8 months, and -9 per cent in 18 months.

In one month there was a slight increase in energy but only slight clinical improvement otherwise. The skin remained very dry. The pulse rate had increased to 86. The

DIABETES MELLITUS

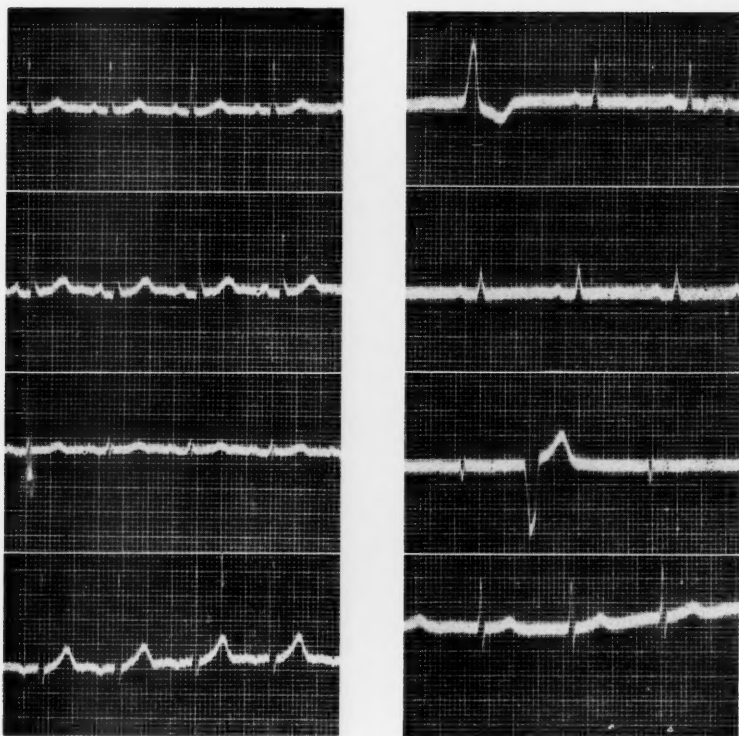


FIG. 1

blood pressure apparently had dropped somewhat and was 120 systolic and 60 diastolic. The tongue, meanwhile, had become quite smooth, and there was deep pitting edema of the ankles. Multi-vitamin capsules and 50 mg. of nicotinic acid t.i.d. were added to her program of treatment. The blood cholesterol already had fallen to 122 mg. per cent.

In two months there was further improvement in strength and energy, the extremities were warmer, and there was less need for sleep. The doughy feeling of the subcutaneous tissues had disappeared, but the skin remained dry. The tongue edges were red, and the pitting edema of the ankles persisted. Her weight had decreased 31 pounds. Thiamine chloride 10 mg. per day was added to her regimen.

In six months almost all the symptoms and signs of myxedema had disappeared. The skin had a normal texture; the blood pressure remained the same; the edema had disappeared; sensory perception in the feet had returned to normal. The tongue remained abnormally red. Her weight was 156 pounds. The memory continued to improve.

There was little further change except that the blood pressure was 136/70 after 9 months and 154/90 after 18 months of treatment. The weight loss was due in part to

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the low caloric intake. A mild hypochromic anemia which appeared in the course of treatment responded to iron therapy.

Course of the diabetes. The diet during the first three months supplied carbohydrate 100 gm., protein 50 gm., and fat 60 gm. per day; total calories 1140. At the beginning of treatment the original diet was followed for four days without insulin. During this time the fasting blood sugar varied from 113 to 246 mg. per cent. Glycosuria was not present, but a further elevation of sugar levels was anticipated because of the action of thyroid. Therefore, protamine zinc insulin was begun in doses of 10 units daily before breakfast. From the third to the eighteenth month, the daily food intake approximated C 160, P 62, F 80, total calories 1752. After 18 months because of an increase in weight from 156 to 169 pounds, the original diet was again prescribed.

In two months blood sugar levels before each of three meals were 165, 164, and 155 mg. per cent. The protamine zinc insulin dose was increased to 15 units daily. Subsequent blood sugar levels before meals were as follows:

	A. M.	Noon	Supper Time
3 months.....	119	104	125
6 months.....	130	103	103
8 months.....	119	106	116
18 months 168 (7 hrs. p.c.).	143 F.	...	171

The rise in blood sugar levels at the eighteenth month examination was subsequent to a period of dietary indiscretion. It indicated that the mild diabetes was still present and had not been changed materially during that period of treatment. The increase in severity of the diabetes due to thyroid probably was balanced by fundamental improvement due to weight loss.



FIG. 2

DIABETES MELLITUS

DIABETES ASSOCIATED WITH ADDISON'S DISEASE

That hypoglycemia occurs in Addison's disease and in adrenalectomized animals has been reported by Bierry and Malloizel in 1908⁷ and Porges in 1909.⁸ Since then the importance of the adrenal in the regulation of carbohydrate metabolism has been demonstrated by Silvette and Britton⁹ in extensive studies on adrenalectomized animals. Long and Lukens¹⁰ have reported experiments on a depancreatized-adrenalectomized dog, which demonstrated the important interrelationship of the adrenals and the pancreas in the regulation of carbohydrate metabolism. After the removal of all adrenal tissue there was a marked decrease in the amount of insulin required to one fourth to one fifth the previous amount. The dog was receiving unfractionated adrenal extract.

Grattan and Jensen demonstrated that the convulsions produced by insulin could be counteracted by the crystalline hormones of the adrenal cortex.¹¹

Kendall¹² stated that in pancreatectomized-adrenalectomized dogs a high degree of glycosuria existed as long as compound E (11-dehydro-17-hydroxycorticosterone) was given. When the administration of this material was stopped, the glycosuria declined to relatively low levels. Attention was directed to the fact that the high degree of glycosuria under these conditions was not associated with extra nitrogen excretion, indicating that the extra glucose did not arise from endogenous protein. This was considered evidence that compound E can suppress the utilization of glucose.

Recent studies of liver glycogen stores in rats treated with various crystalline adrenal cortical preparations have demonstrated an extreme variation in effect. No increase in liver glycogen was observed following treatment with very large doses of desoxycorticosterone acetate, while a marked increase occurred following very much smaller doses of corticosterone, 17 hydroxy-11-dehydrocorticosterone and 17-hydroxycorticosterone. The injection of unfractionated adrenal extracts in large doses also resulted in a marked increase in liver glycogen.¹¹

Only a few of the many interesting interrelationships of adrenal cortical hormones and carbohydrate metabolism have been mentioned. Clinically, the types of cases which represent the diabetic tendency associated with adrenal cortical hyperactivity are Cushing's syndrome, adreno-genital syndrome, Achard-Thiers syndrome (diabetes of bearded women), and some cases of adrenal cortical tumor.

The reported cases in which diabetes and Addison's disease have been coexistent are very few. Bloomfield¹³ reviewed the cases up to 1939

(4 cases) and reported a case of diabetes which subsequently developed Addison's disease. During the development of the Addison's disease the insulin requirement decreased from 40 units to 4 to 6 units. Treatment with desoxycorticosterone acetate did not modify the diabetic state, but treatment with adrenal extract (Eschatin) was followed by a greater hyperglycemia and increased glycosuria.

Case 2. (Patient referred by Dr. W. A. Klann, Wellington, Ohio) On May 4, 1942 a pale thin young man presented himself complaining chiefly of weakness, persistent left abdominal and epigastric pain, anorexia, and a loss of 30 pounds in six months.

The presence of diabetes had been known for seven years. It had been ushered in with cardinal symptoms and had been treated with diet and insulin. In 1940 he had been taking 40 units of protamine zinc insulin daily. This had been discontinued for several months but had been started again because of increasing symptoms.

Since January 1942 he had spent from several days to several weeks in three hospitals where attempts had been made to control his diabetes. The diet had varied, and insulin doses sometimes had been as low as 40 units, at times as high as 120, and recently 80 units of protamine zinc insulin per day.

As long as three years ago peculiar reddish areas had begun to appear on both shins. In the late summer of 1940 following a minor injury to his right shin a very large painless ulcer had appeared involving two-thirds of the length of his right shin. About January, 1942 a similar large ulcer formed on the left shin. In addition there were several yellowish purple areas of smaller size and irregular shape which appeared for a time on the verge of necrosis but did not ulcerate. The large ulcers healed completely following periods of improved diabetic control.

In January, 1941 he had begun to notice soreness and dull pain in the epigastrium and at times pain in the left groin extending downward toward the testis. The epigastric pain was somewhat relieved by bowel movement, but was not related to meals or to urinary symptoms. The appetite had become increasingly poor, amounting almost to a disgust for food, and he had lost 30 pounds in weight during this time. He was very constipated.

Physical examination. The patient was thin and pale. He appeared weak, dehydrated, somewhat drowsy, and obviously was very ill. His height was 69¾ inches; weight 120 pounds clothed; temperature, 98.6° F.; pulse 80; blood pressure 100 systolic and 70 diastolic. Except for evident malnutrition and dehydration, there were few noteworthy physical findings. The skin was dry and sallow, and the mucosae were dry. There were a few shotty glands in the inguinal regions. There was mild tenderness to pressure in the region of the mid-epigastrium and the sigmoid colon. No pigmentary changes of the skin were noted. Rectal examination was normal, and the reflexes were intact. Retrospective examination of the skin and mucous membranes showed no abnormal pigmentation of the buccal mucosae nor skin and no black freckles, although the patient believes that many small moles have become darker than they had been previously. The large reddish or brownish red atrophic scars of the legs, because of their peculiar relationship to the diabetes, are described below in more detail.

Because the patient was very ill and because relatively severe diabetic acidosis was strongly suspected, he was admitted to the hospital at once for treatment, and further investigation considered not immediately necessary was postponed.

DIABETES MELLITUS

Immediate course. Urinalysis for sugar and acetone was ordered, and the immediate determination of blood sugar and CO₂ combining power. Arrangements were made for one of the technicians to stay on duty all night in the event that the CO₂ combining power were found to be below 30. We were astonished to find that the urine contained no ketone bodies, and the CO₂ combining power was 55.7 volumes per cent. The blood sugar level was 348 mg. per cent. A liquid diet was ordered to supply C 100, P 50, F 60 within 24 hours. One thousand cc. of 1 per cent normal saline intravenously, and 50 units of protamine zinc insulin and 40 units of regular (amorphous) insulin were given. After four and a quarter hours the blood sugar was 89 mg. per cent. The following morning the blood urea was 36 mg. per cent, cholesterol 189, CO₂ combining power 38.5 volumes per cent.

The diet, blood sugar, and insulin doses for the next three days are shown in the following table. The four periods of the day represent periods before meals and at bed-time, and blood sugar levels are fasting or approximately four hours after food unless otherwise stated. 'P' designates protamine zinc insulin, and 'R' regular (amorphous) insulin.

TABLE 1

Date	Blood Sugar mg. % (Hr. P.C.)	Insulin	Diet Taken			
			C	P	F	Cal.
May 5						
1	78(F)	30 P				
2	227(4)					
3	208(4)	4 R				
4	202(4½)		198	60	95	1887
May 6						
1	128(F)	30 P 5 R				
2		5 R				
3	92(4)	5 R				
4			193	54	86	1682
May 7						
1	50(F)	30 P 5 R				
2						
3	70(4½)	6 R	170	74	120	2136
4						

During the next few days the patient improved markedly but remained weak. He ate the prescribed quantities of food with much difficulty and continued to complain of epigastric pain. The diet was concentrated, of smooth quality, and increased in caloric value. He was given phenobarbital and tincture of belladonna to tolerance,

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almost continuous heat to the abdomen, and small saline enemas after breakfast if necessary.

It soon was apparent that the diabetes was extremely erratic. We were now obliged to devise a scheme whereby the patient might hope to control his diabetes at home. For this purpose urine specimens secreted during the half-hour before meals and before bed-time were tested, and regular insulin was added at various times of day in amounts of 6, 10, or 12 units for yellow, orange, or red Benedict's qualitative reactions respectively. Such a plan improved his control, but frequent blood sugar determinations clearly demonstrated its relative inefficiency in this case. Some of the diabetic data from the 11th through the 15th hospital days are shown below.

TABLE 2

Date	Blood Sugar mg. % (Hr. P.C.)	Insulin	Diet Taken			
			C	P	F	Cal.
May 15						
1	56(F)	34P 10R				
2						
3	240(4)					
4	375(4¼)	4R	245	42	105	2109
May 16						
1	309(F)	34P 4R				
2		10R				
3						
4			227	62	114	2182
May 18						
1	92(F)	34P 3R				
2	103(4)					
3	146(3¾)	3R				
4	108(4¼)		230	46	109	2085
May 19						
1	73(F)	34P 3R				
2						
3	300(4)	6R				
4	254(4¼)	3R	240	47	97	2021

The patient was dismissed on the 20th hospital day.

Special examinations and laboratory reports. (Dermatological, Dr. E. W. Netherton) During the past three years small red lesions had appeared without trauma on both lower legs. Some had enlarged slowly, some rapidly, by peripheral extension to form rounded and irregular brownish red areas of variable size. The larger lesions were ulcerated. There was a long band-like, indolent, brownish red, well-defined plaque 9¼ by 2¼ inches on the anterior surface of the right leg. This extended from just be-

DIABETES MELLITUS

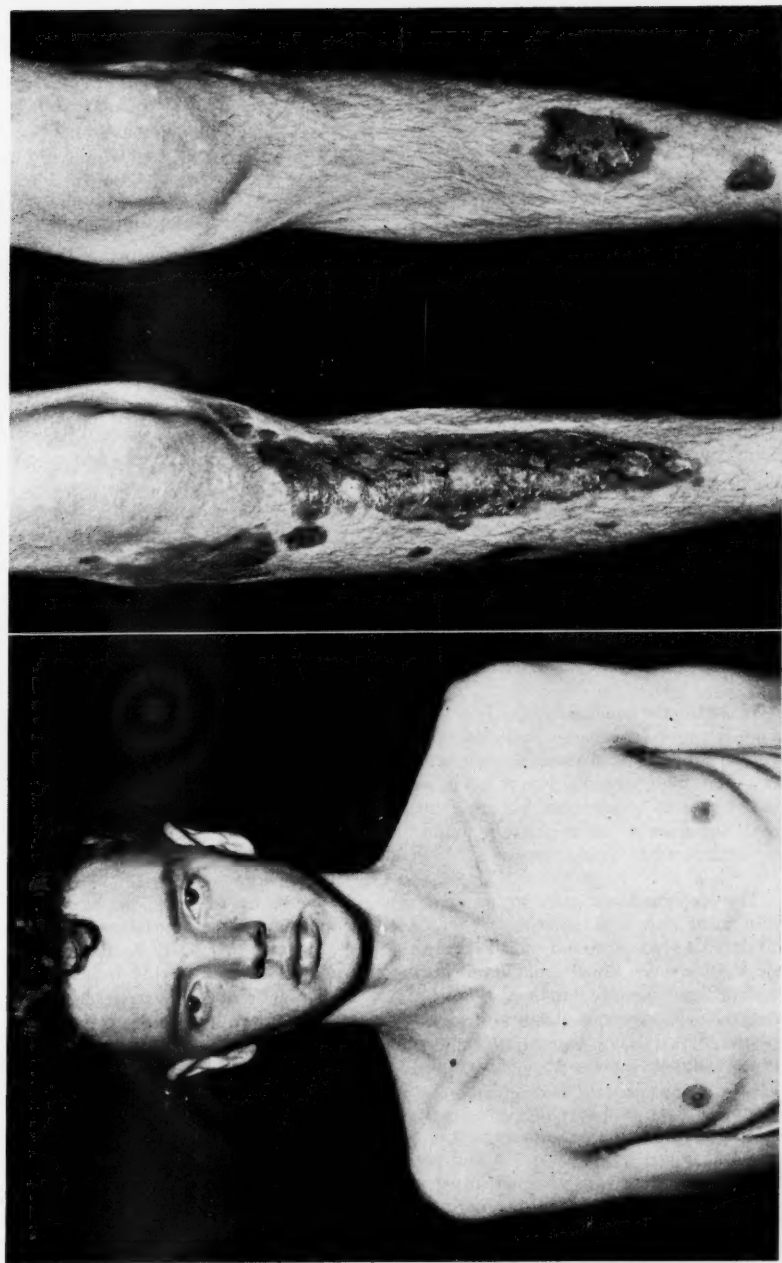


FIG. 3

low the knee to about the junction of the 2nd and 3rd third of the leg and was located over the anterior portion of the tibia. The central portion of the lesion was an atrophic scar, while the periphery was slightly thickened by a yellowish or xanthomatous deposit in the skin. There was telangiectasia over the margin of the lesion, and fairly large, thin, brown, adherent scales were scattered over the lesion. There were smaller rounded or irregular lesions of a similar nature on the lateral surfaces of the right leg and also a few lesions on lateral and anterior surfaces of the left leg. There were no lesions above the knees. The striking features were the atrophic scarring (tissue destruction), chronicity, and the xanthomatous deposit in the lesions. Diagnosis: necrobiosis lipiodica diabetorum.

X-rays. An intravenous urogram was normal. Gastrointestinal x-rays revealed a normally functioning gallbladder without stones. The stomach was large and showed a 15 per cent retention after four and one-half hours. The third portion of the duodenum was dilated. Partial duodenojejunal obstruction possibly due to congenital bands was suspected.

The blood counts were normal; blood urea 30 mg. per cent; Wassermann and Kahn tests negative; serum proteins totaled 7.2; albumin 4.9; globulin 2.3 grams per cent. Fractional test meal showed normal gastric acidity.

Continued rest, smooth diet, heat to the abdomen, the use of sedatives and antispasmodics, and regular emptying of the bowel failed to bring more than the slightest symptomatic relief. Five days later the patient returned to the office with the same complaints, having lost an additional seven pounds in weight since his first admission. Extenuating circumstances rendered further gastrointestinal investigation impossible, and, although neither gastrointestinal nor surgical consultants were at all enthusiastic, exploratory laparotomy was prescribed.

Second hospital admission. On June 1st the patient was readmitted to the hospital. His preoperative preparation included 10 to 20 grams of sodium chloride intravenously daily. On June 5th laparotomy was performed. No duodenal obstruction could be found. Many small hypertrophied lymph nodes were seen at the root of the mesentery. Those removed showed hyperplasia but no evidence of tuberculosis. The appendix was removed, and since no cause could be found for the abdominal distress, cholecystostomy was performed.

The postoperative course was relatively smooth. One thousand cc. of 5 per cent glucose in saline was given intravenously on the day of operation and on the following day. Considerable glycosuria and mild ketonuria appeared on the second, third, and fourth postoperative days. Blood sugar levels during this period varied from 150 to 256 mg. per cent. Blood pressure remained about 110 systolic and 80 diastolic, the pulse approximately 120. Intravenous glucose in saline was not given from the second to the fifth postoperative day. The patient appeared unusually listless and could be persuaded to take nourishment only with considerable difficulty.

On the sixth and seventh days 5 per cent glucose in 1 per cent saline was given intravenously, and the patient seemed to show a more marked symptomatic response than usual. Blood sodium was 354 and potassium 16.0 mg. per cent. On examination of the daily chloride excretion, we suspected that he was retaining blood chlorides with abnormal difficulty. It was at this point that Addison's disease was seriously suspected, and Kepler's adrenal function test was ordered.

DIABETES MELLITUS

The amounts of urine excreted were as follows:

10:30 p. m. to 7:30 a. m.....	605 cc.
8:30 a. m.....	62 cc.
9:30 a. m.....	143 cc.
10:30 a. m.....	313 cc.
11:30 a. m.....	386 cc.
12:30 p. m.....	94 cc.

Because the highest volume of any of the morning specimens was exceeded by the night specimen, this part of the test ("the water test") was positive and favored adrenal failure. The blood chloride level during the test fell to 495 mg. per cent. There was a trace of sugar in the urine at bedtime on the evening the test was begun, and none the next day at noon. Diabetic polyuria, therefore, was not a factor.

On June 19th, the 16th day postoperative, the patient was given 15 cc. of adrenal cortical extract subcutaneously in three doses, 1000 cc. of 5 per cent glucose in 1 per cent saline intravenously, and 5.0 mg. of desoxycorticosterone acetate intramuscularly. Subsequently, he was given 6.0 gm. of NaCl in enteric coated pills daily and 5.0 mg. of desoxycorticosterone acetate daily which later was reduced to 2.5 mg. The response was dramatic. Within two days his strength had improved markedly, and within the next few days his appetite was good. Within about 10 days the abdominal distress disappeared. Blood sodium on July 15, 1942 was 354 and potassium 16.0.

After the treatment had been followed for fifteen days it was discontinued for three days and Kepler's test was repeated. The water excretion was as follows:

10:30 p. m. to 7:30 a. m.....	222 cc.
8:30 a. m.....	6 cc.
9:30 a. m.....	9 cc.
10:30 a. m.....	21 cc.
11:30 a. m.....	64 cc.
12:30 p. m.....	55 cc.

The second procedure was calculated as follows:

$$\frac{\text{Urinary urea } 225 \text{ mg. } \%}{\text{blood urea } 57 \text{ mg. } \%} \times \frac{\text{Blood chlorides } 495 \text{ mg. } \%}{\text{urinary chlorides } 808 \text{ mg. } \%} \times \frac{\text{Largest 1 hr. vol. day urine } 64 \text{ cc.}}{\text{volume night urine } 222} = 6.9$$

Any factor below 25 is considered positive.

At the end of this test the blood urea had risen to 57 mg. per cent, and the blood chlorides had fallen to 495 mg. per cent. The blood pressure was 80 systolic and 60 diastolic. He was very weak, and he found it difficult to stand or walk. The anorexia had returned. Again following intravenous saline, cortical extract and "desoxy" he was almost completely rehabilitated overnight. At present his progress is excellent. X-rays of the adrenal areas showed no evidence of calcification. Chest x-rays demonstrated no signs of tuberculosis.

Final diagnoses. Diabetes mellitus, necrobiosis lipoidica diabetorum, Addison's disease.

The subsequent treatment in this case will include, firstly, a determination of the optimum dose of desoxycorticosterone acetate by continued use for an additional three weeks. After that it is planned that he will receive an implantation of pellets of "desoxy." If Schering's pellets are used, he will receive approximately 1.0 mg. per day from each 300 mg. implanted, and each 1.0 mg. per day absorbed from the implant has the approximate value to the patient of 2.0 mg. by injection. If the implant proves to be delivering too much hormone and abnormal retention of water is indicated by edema or by blood dilution (hematocrit, proteins, calcium, etc.), the amount of salt will be reduced. If it proves insufficient, more salt will be given.

Later we hope to study the possible stabilizing effect of adrenal cortical extract in this type of diabetes.

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THE WELTMANN REACTION IN PULMONARY TUBERCULOSIS

W. F. OWEN, Jr., M. D. and H. S. VanORDSTRAND, M. D.

INTRODUCTION

In 1930, Oskar Weltmann¹ introduced a new serum coagulation reaction to distinguish exudative from fibrotic processes in the body, and since its discovery, it has been employed routinely in many European Clinics. There is a great deal of valuable literature on the subject, but singularly enough, very little is reported in the American literature. It is the purpose of this study to determine the value of the Weltmann reaction in establishing the diagnosis of active pulmonary tuberculosis and in following the progress of such cases.

TECHNIC

The test is simple to perform and requires very little apparatus. The result can be determined within 20 to 25 minutes. From a stock 10 per cent calcium chloride solution ($\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$), ten dilutions are made up, varying from 0.1 per cent to 0.01 per cent. Five cc. of each dilution is pipetted into each of ten tubes. Ordinary Wassermann tubes may be used, and the tubes numbered from 1 to 10, beginning with the strongest dilution. Into each tube pipette $1/10$ of a cc. of the unhemolyzed serum to be tested. The contents are mixed thoroughly and the tubes placed in a boiling water bath for 15 minutes. They then are removed, and the test is read. The contents of the tubes may be clear, faintly opalescent, turbid, or there may be flocculation. The number of tubes in which flocculation occurs is designated by Weltmann as the coagulation band of the particular serum tested, i.e., W. C. B. = number of tubes showing flocculation. If there is very slight or doubtful flocculation in one tube, the reaction is interpreted as being intermediate. Usually, the difference between turbidity and flocculation is very sharp. The only really important precaution is to be sure that the serum is unhemolyzed. In the experience of the writers hemolysis always increases the number of tubes showing flocculation and therefore gives an inaccurate result. It has been found by other authors that irradiation, freezing, inactivation at 56°C ., and storage for two to three days has no effect on the coagulation band. Therefore, the test is relatively stable. In normal sera the first six tubes show flocculation. Occasionally, there is a slight degree of flocculation in the seventh tube. The normal coagu-

lation band then is 6 to 6½. In his original article Weltmann stated that if the coagulation band (C. B.) was less than 6, the reaction showed a "shift to the left" and when the C. B. was 7 or more, a "shift to the right" was indicated.

MECHANISM AND INTERPRETATION

The exact nature of the chemical or physico-chemical mechanism of the Weltmann reaction has not yet been determined. Likewise, very little is known of the changes occurring in the heat coagulation of proteins. Weltmann¹ originally thought that the basis of the reaction lay in the coagulation of serum albumin by heat in the presence of electrolytes. Massobrio and de Michelis² were the first to claim that the serum proteins had an effect on the coagulation band, and that a "shift to the left" occurred when the albumin fraction was decreased and the globulin fraction was increased. This view did not coincide with the work of later investigators including Levinson and Klein,³ who found that in nephrosis, when the albumin-globulin ratio was reversed, there was an extreme "shift to the left," while in cirrhosis, when there was always a "shift to the right," there was also at times a reversal of the albumin-globulin ratio. Levinson and Klein³ showed that the hydrogen ion concentrations of the solutions used in the test played no part in the reaction. In a small number of cases they apparently found some correlation between the blood pH and the coagulation band, for as the coagulation band lengthened, the pH shifted toward the acid side, while a more alkaline pH was usually accompanied by a shorter coagulation band. Kretz and Kudlac⁴ found that the calcium and chloride content of the serum used had no effect on the C. B., while Dees⁵ claimed that calcium was essential for the reaction to take place. She found no coagulation when calcium was removed from the system by a sulfonated fatty acid, which had a marked affinity for calcium. Dees was also able to increase the coagulation band two hours after the intravenous injection of 5 cc. of 10 per cent calcium chloride solution. Levinson and Klein³ found no correlation between the level of blood cholesterol and the length of the band. In spite of our poor appreciation of its mechanism, the Weltmann reaction has been found to be of clinical value.

OBSERVATIONS OF OTHER INVESTIGATORS

Levinson and Klein,³ in 1938, studied the Weltmann reaction in cases of pulmonary tuberculosis for a period of three to five months and concluded that there was no definite correlation between the Weltmann

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reaction and the sedimentation rate, and that the former seemed to be a better index of the clinical state of the patient.

Makitra and Tyndel⁶ determined the Weltmann C. B. in 200 patients with pulmonary tuberculosis, and their results indicated that in incipient cases of exudative tuberculosis the coagulation band gave more reliable results than the sedimentation rate. These authors stated that the Weltmann reaction could be used prognostically in chronic tuberculosis. They claimed that the sedimentation rate responded readily to the slightest alterations in the body and was less stable than the coagulation band.

Voigtlander,⁷ in 1934, reported 400 cases of tuberculosis, which he followed in a sanatorium. He concluded that the test was valuable in the diagnosis and prognosis of tuberculosis, and that it was a most important aid in determining whether fibrosis or exudation was present in the lung.

Dissmann,⁸ in 1934, did the Weltmann test on 274 tuberculous patients and compared the results with tests on normal individuals. He found the degree of a "shift to the left" to correlate quite closely with the severity of the exudative process present. He also found that in the presence of fibrocaceous tuberculosis and fibro-ulcerative tuberculosis the coagulation band was frequently normal. A "shift to the right" was noted in only purely productive lesions, i.e., in the closed cavity and healing stages.

In his original study Weltmann¹ made no claim that the coagulation band was specific for any disease. He committed himself only by saying that the test was of value in distinguishing between exudative and productive processes.

STUDY OF THE WELTMANN REACTION IN 85 NORMAL INDIVIDUALS AND 75 PATIENTS WITH PULMONARY TUBERCULOSIS

Before applying the Weltmann reaction to cases of pulmonary tuberculosis, it was necessary to determine the reaction of normal sera to the test. Therefore, the Weltmann reaction was determined in 85 normal individuals. This group included doctors, nurses, and medical students, all of whom were known to be normal and in whom negative chest x-rays had recently been taken. In all instances the Weltmann coagulation band was found to be 6 to 6½. This figure is in complete agreement with the normal bands reported by other investigators. A total of 75 cases of pulmonary tuberculosis was then observed. Twenty-five of these were classified as moderately advanced and far advanced,

chronic, inactive. The remaining 50 included 27 far advanced, 20 moderately advanced, and three minimal.

In the 27 far advanced cases the following results were obtained. In 14 cases the Weltmann coagulation bands reflected the clinical course of the patient, and in 13, or about 50 per cent, the test was not correlated with the clinical picture. One of these patients with a coagulation band of 8 died. In these same patients the sedimentation rate was also observed. In 23 of the 27 cases, or 84 per cent, the sedimentation rate followed the clinical course of the patient, and in four cases, or 16 per cent, it was without significance. Most of the patients in this group had both productive and exudative processes occurring simultaneously in the lung, although from observations of the temperature, pulse, and chest x-rays the predominant process could usually be determined. In this group, therefore, the Weltmann coagulation band was of value in only 50 per cent of the cases, while the sedimentation rate was a valuable guide in 84 per cent.

Twenty cases were observed in the moderately advanced group. In 16 of these, or 80 per cent, the Weltmann test mirrored the clinical activity, while in four cases, or 20 per cent, it did not. Again the sedimentation rate was determined and only in 12 cases, or 60 per cent, did it correlate with the clinical status of the patient. In 40 per cent, or in eight cases, it was of value. In this group, therefore, the coagulation band seemed of more value than the sedimentation rate.

Minimal group. There were only three cases in this group and the sedimentation rate was of no value, while the Weltmann coagulation band was a valuable guide in all. Two of these patients had minimal, soft appearing lesions in the apices without symptoms. In both the coagulation band was 5, and with clinical improvement and diminution in the size of the lesions by x-ray the band returned to normal. In the third case x-ray showed only a hard, calcific appearing lesion. The temperature and pulse were normal, and the coagulation band varied between 6 and 7. In the first two cases the sedimentation rate was rapid at the start and continued to be rapid even when x-ray and clinical signs showed healing. The sedimentation rate was rapid in the third case when all other examinations showed the lesion to be inactive and old. Of the 50 cases studied and followed over a period of months, the Weltmann coagulation band was consistent with the clinical and x-ray status of the patient in only 32 cases, or 64 per cent, while the sedimentation rate was in agreement in 40 cases, or 79 per cent. There was no definite correlation between the Weltmann coagulation band and the sedimentation rate.

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CASE REPORTS

Case 1. A 32 year old colored woman complained of a "cold" of a month's duration characterized by cough, productive of one-half cupful of mucopurulent sputum per day. She had also had low grade afternoon fever and night-sweats, although she had had no hemoptysis nor pleuritic pain.

Physical Examination. The patient was thin and appeared to be chronically ill. Examination of the lungs revealed dullness in both apices anteriorly and posteriorly and many fine dry râles over the same areas. X-ray showed a dense infiltration involving the left apex and subapical region. There was a questionable cavity on the left below the clavicle. The diagnosis was moderately advanced pulmonary tuberculosis with probable cavitation on the left. The sputum was positive for acid-fast bacilli, and successive counts showed Gaffky III, IV and IV. The temperature varied between 38° C. (100.4° F.) and 39° C. (102.2° F.); the pulse was 90-100. At the time of admission the sedimentation rate was 1.30 mm. per minute and W. C. B. 6. Later coagulation bands failed to change from the original figure. Obviously, this was an active, moderately advanced case of pulmonary tuberculosis, and the sedimentation rate was a far better guide than the Weltmann coagulation band.

Case 2. A 21 year old white woman was admitted because an x-ray of the chest made two weeks previously showed a "spot" on the right lung. A brother, during an army examination, had been found to have tuberculosis. For one month the patient had had a cough productive of a small amount of white sputum. Also, for this period she had had a "stitching" pain in the right chest, which was worse upon taking a deep breath. There was no history of fever, hemoptysis, night-sweats, or weight loss. The physical examination was completely negative, and x-ray of the chest showed a "soft infiltration" in both apices and right subapical area. There was no evidence of cavitation. The diagnosis was moderately advanced pulmonary tuberculosis. Sputum was negative for acid-fast bacilli on five occasions. Temperature remained steady at 37° C. (98.6° F.) and pulse 80 with several rises to 100. The sedimentation rate on admission was 0.24 mm. per minute and coagulation band was 4. Here, we believe, the Weltmann coagulation band showed correctly a "shift to the left" indicating an exudative type of process in the lungs. Here again, there was no correlation between the sedimentation rate and the coagulation band.

Case 3. A 23 year old white woman complained of having lost 30 pounds during the eight months before admission. Four months before admission, she had developed a cough productive of small amounts of mucopurulent sputum daily, weakness, and afternoon fever. Physical examination showed a chronically ill, emaciated woman in no particular distress. Examination of the lungs showed dullness and post-tussive râles over the left apex anteriorly and over both apices posteriorly. X-ray was interpreted as showing moderately dense mottling and linear shadows in the upper half of both lung fields. On both sides there was one or more thin-walled cavities in the range of 2-4 cm. in diameter. The shadows indicated a mixture of exudative and proliferative disease. The diagnosis was far advanced pulmonary tuberculosis. Sputum-Gaffky II—temperature ranged between 37.5° C. (99.5° F.) and 38.5° C. (101.3° F.), and pulse 90-100. The sedimentation rate was 1.54 mm. per minute and Weltmann coagulation band 5. Here is an instance of agreement between the two tests, in which both reflected the clinical picture.

Case 4. A 27 year old white woman was diagnosed as having pulmonary tuberculosis in 1933. She had spent 20 months in a sanatorium, and while there, pneumothorax had begun on the left and was continued with 300 to 500 cc. every two weeks thereafter.

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She had been referred to the hospital because x-ray had shown an area suspected of being tuberculous on the right. There had been no complaints. The patient was well developed and well nourished and did not appear ill. Examination of the lungs showed fine dry râles, decreased tactile fremitus, and breath sounds over the left anterior chest. There were some post-tussive râles over the right anterior chest. X-ray showed a 50 per cent pneumothorax on the left with an adherent apex. There was a small amount of calcified infiltration in the apex of the left lung and upper one-third on the right. No cavities were seen. The diagnosis was pulmonary tuberculosis, moderately advanced with an artificial pneumothorax (left). Sputum was negative for acid-fast organisms on three examinations. Temperature ranged between 37° C. (98.6° F.) and 37.5° C. (99.5° F.), pulse 80-90. The sedimentation rate was 0.67 mm. per minute and coagulation band 7. The clinical picture was that of chronic inactive tuberculosis, and the Weltmann showed a slight "shift to the right" indicating a predominance of fibrosis. The sedimentation rate here agreed neither with the Weltmann reaction nor with the clinical picture.

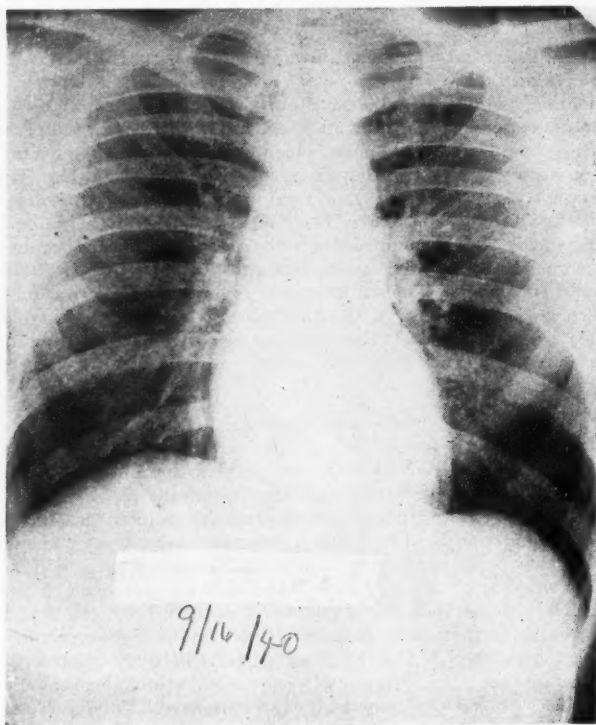


FIGURE 1. X-ray of the chest taken on admission on 9/16/40. This was interpreted as being essentially normal save for rather heavy hilar shadows. The sedimentation rate was rapid, and the Weltmann coagulation band = 4.

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Case 5. A 17 year old colored girl had had a "bad cold" for the five weeks preceding admission. There had been no hemoptysis, weight loss, nor pleuritic pain. Physical examination revealed post-tussive râles over the left apex anteriorly and posteriorly. On the right there were post-tussive fine dry râles and distant breath sounds over the apex anteriorly and posteriorly. X-ray showed a conglomerate patch of infiltration filling the second anterior interspace and extending over adjacent ribs on the right. On the left a patch of infiltration overlying the first interspace and adjacent ribs and a smaller area along the course of the eighth posterior rib. There were no definite cavities. The diagnosis was pulmonary tuberculosis, moderately advanced. A bilateral pneumothorax was contemplated, and this was started on the left side one week following admission (2/14/42). Sputum examination showed the following: 2/2/42, negative—2/7/42, Gaffky III—2/9/42, Gaffky II—2/11/42, Gaffky II—3/2/42, negative. The temperature remained at 37° C. (98.6° F.) with an occasional rise to 37.5° C. (99.5° F.), pulse 80-100, and remained steady at 80 following the pneumothorax. The sedimentation rate on admission was 1.36 mm. per minute and coagulation band 8.

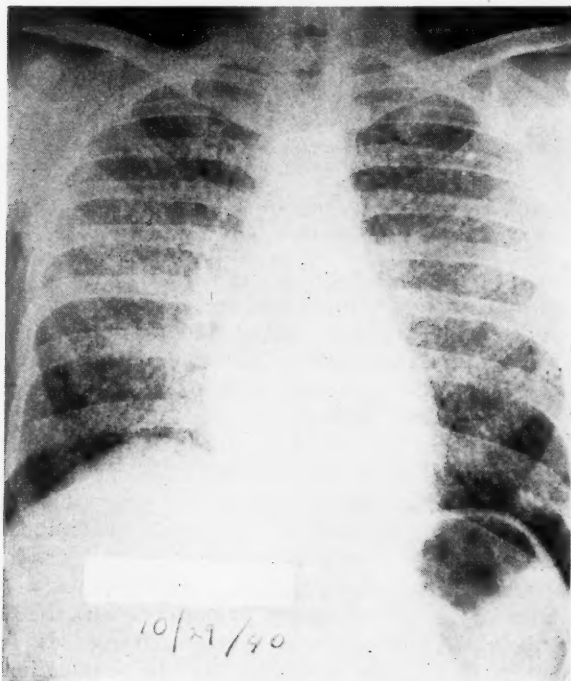


FIGURE 2. X-ray of the chest taken one week before death interpreted as showing miliary tuberculosis, later proved at autopsy. The sedimentation rate was very much elevated, and the Weltmann coagulation band = 0.

This case illustrates again the lack of correlation between the two tests, and in this particular instance the value of the sedimentation rate over the coagulation band.

Case 6. A 27 year old colored handy-man had been well until three weeks before admission, when he complained of general malaise and mild frontal headache. The last week before admission, he had also complained of fatigue and anorexia. On admission the temperature was 37.5° C. (99.5° F.), pulse 70, and respiration 20. General appearance was that of a well developed, well nourished colored man who did not appear acutely ill. There were no positive physical findings. A diagnosis of miliary tuberculosis was suggested. Laboratory findings were within normal limits except for a white blood count of 3,600. During the first week of admission, he ran a low grade afternoon fever together with a relatively slow pulse. Examination of the lungs showed a few coarse moist bilateral basilar râles. X-ray taken in the first week of hospitalization is shown in Figure 1. During the following month his temperature ranged around 39° C. (102.2° F.), and pulse 70-80. He lost 20 pounds in weight, and his appetite was poor. There was no cough, but he had drenching night-sweats. A film taken one week before death and four weeks following the first x-ray is shown in Figure 2. During the week before death occurred, the lungs were full of coarse moist râles, and he was dyspneic and orthopneic. A miliary tubercle was seen in the fundus of the right eye. At autopsy miliary tubercles were found in the lungs, liver, spleen, kidneys, and right eye.

The sedimentation rate remained elevated throughout, and the coagulation band showed a consistent "shift to the left," finally falling to 0.

SUMMARY

The Weltmann coagulation band was determined in 85 normal individuals and a remarkably constant result obtained, i.e., $6-6\frac{1}{2}$.

In 75 cases of pulmonary tuberculosis, followed for a period of three to four months, an attempt was made to define how closely the coagulation band reflected the clinical picture and whether there was any correlation between the band and the sedimentation rate. In this group of 75 cases, 25 were chronic, arrested, inactive cases, and here the Weltmann reaction consistently showed a "shift to the right" and was a better indication of the clinical status than the sedimentation rate. In the remaining 50 cases the Weltmann coagulation band followed the clinical picture in 32 cases, or only 64 per cent, while the sedimentation rate was a good index in 40 cases, or 79 per cent. When the cases were divided into far advanced, moderately advanced, and minimal, it was shown that in the 27 far advanced cases, the Weltmann reaction was reliable in only 50 per cent as against 84 per cent with the sedimentation test. In the moderately advanced group of 20 cases, the sedimentation rate showed 60 per cent reliability and the coagulation band 80 per cent. There were only three minimal cases studied, and the sedimentation rate was of no value in any while the Weltmann test was reliable in all.

WELTMANN REACTION IN PULMONARY TUBERCULOSIS

CONCLUSION

1. Neither the Weltmann reaction nor the sedimentation rate is completely reliable or infallible in the diagnosis and prognosis of pulmonary tuberculosis. In these cases the sedimentation rate has been a somewhat better index of the clinical status of the patient. In doubtful cases it may be of value to do both tests.

2. In the chronic, arrested, inactive cases the Weltmann reaction consistently showed a "shift to the right" and was a better indication of the clinical status than the sedimentation rate.

3. There is no definite correlation between the Weltmann coagulation band and the sedimentation rate.

The authors are indebted to Dr. R. C. McKay and Dr. J. B. Stocklen for the privilege of using the Cleveland City Hospital and the County Tuberculosis Dispensary for material for this study.

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HODGKIN'S DISEASE

Review of 47 Cases

RUSSELL L. HADEN, M.D. and JAMES T. BURNS, M.D.

Hodgkin's disease is a "specific general disease of a malignant character in which any organ or tissue of the body may be affected." (Osler) While the disease begins characteristically with enlargement of the cervical lymph nodes, other nodes may be affected first, or the primary lesion may be an infiltrating one elsewhere. Various specific organisms have been recovered from involved tissue. The consensus of opinion is that these are secondary invaders. The disease is most likely neoplastic in origin. Tuberculosis is often associated with Hodgkin's disease, but has no causal relationship with it. The disease, unlike lymphosarcoma and leukemia, with which it is often confused and even grouped by some pathologists, has never been identified in lower animals.

The clinical picture of Hodgkin's disease is extremely variable. The most characteristic course is primarily a slow and progressive, painless enlargement of the cervical lymph nodes often beginning on one side of the neck only. The nodes are discrete and firm. Later other nodes are usually involved, and still later fever, anemia, and cachexia set in causing the death of the patient. All variations of this picture may be observed. Fever and anemia may be the first and only presenting symptoms, especially when the lesion is primarily infiltrative. It is common to find only the peribronchial glands involved, often with infiltration of the lungs. Since any part of the body may be affected, the possibility of Hodgkin's disease must be considered in many confused clinical states, especially with cryptic fever and anemia.

From 1930 to 1940 the diagnosis of Hodgkin's disease was made in the Cleveland Clinic in 90 patients. A group of 47 patients in whom the diagnosis was established by biopsy or autopsy has been selected for this clinical study. In every patient the clinical result and final outcome are known. In many cases patients were seen after a biopsy elsewhere or after irradiation with resultant disappearance of the glands which made a biopsy impossible. In other cases the diagnosis was based upon x-rays of the chest or on clinical grounds without substantiation by pathological study of a lymph gland or other tissue. Since such diagnoses are always open to question, these have been excluded. We have also not included any case without an adequate follow-up.

Ten patients complained only of such general symptoms as weakness, fever, pain in different parts of the body, weight loss, dyspnea, and

HODGKIN'S DISEASE

anorexia. Nine of the ten patients had definite enlargement of the lymph glands, although this was not marked and was not recognized by the patient. Thirty-seven patients complained of swollen glands, usually in the neck and often associated with general symptoms such as those described by the first group.

Twenty-five of the entire group were men and 22 were women. The youngest patient was $3\frac{1}{2}$ years of age and the oldest 67 years. Nine patients were less than 20 years of age, and five were over 60. Nineteen patients were in the 20-40 age group and fourteen in the 40-60 age group. The average age of the entire group of patients was 35 years.

The pain complained of was at times severe, probably due to the infiltration of tissues by the Hodgkin's disease. In one patient severe interscapular pain was followed in two weeks by a hydrothorax. In another the pain in the shoulder, arm, and chest was so severe that a cordotomy was considered. Infiltration of the spinal cord with extreme pain has been observed.

Thirty-two of the 37 patients who complained of glandular enlargement first noticed the gland involvement in the neck. In five patients the primary swelling was in the inguinal or axillary regions. Enlarged axillary glands were usually present although often not apparent in the patient.

The spleen was palpable in 17 patients although seldom greatly enlarged. The liver was enlarged in six instances. Ascites was present in five patients.

The blood count often showed an anemia, usually of the hypochromic or iron deficiency type. In eight patients the hemoglobin was above 80 per cent. In the remaining 39 patients the average hemoglobin was 65 per cent (10.0 gm.). The lowest reading observed when the patient was first seen was 39 per cent (6.0 gm.). The white cell count was below 10,000 in 22 patients, above 20,000 in three patients, and between 10,000 and 20,000 in 22 patients. The differential count was normal in the group of patients with a total count less than 10,000. As the white count increased, there was an increase in the polymorphonuclear neutrophile percentage with a decrease in the lymphocytes and monocytes. It is apparent that there is nothing characteristic in the blood count.

Chest x-rays were taken in most instances. Enlarged hilar glands, hilar and lung infiltration, and masses in the lungs were often found, usually without symptoms referable to the chest.

Five patients are known to be living two, five, six, seven, and eight years after first being seen. Forty-two are known to be dead. The average length of life was two and one-half years. One patient lived nearly ten years, and six others lived five years and over. It is apparent that a prognosis as to length of life in Hodgkin's disease is very hazardous. Most of the patients were treated by irradiation. The response to such treatment is usually very gratifying at the outset. The time always comes, however, when irradiation does not relieve the patient. Death is often due to fever, anemia, and cachexia without the reappearance of lymph gland enlargement.

Three of the five patients who are living five, seven, and eight years after the diagnosis were treated by irradiation and show no signs of the disease. In one patient the disease has been recurrent and is again being treated. One patient has become insane.

SUMMARY AND CONCLUSIONS

Forty-seven patients with Hodgkin's disease in whom the diagnosis was made by the examination of biopsied lymph glands or other tissue and in whom the ultimate result is known are reported.

Forty-two patients are dead. The average length of life was two and one-half years.

Five patients are living two, five, six, seven, and eight years after first being seen. One has had a recurrence.

All patients had glandular enlargement although unrecognized by ten.

The cervical glands are most commonly involved and often without lymphadenopathy elsewhere at the onset.

Other common symptoms are pain, anemia, and fever. The spleen was palpable in 36 per cent of the cases. The leukocyte count often shows a polymorphonuclear leukocytosis, but this is not constant or diagnostic. The diagnosis can be made with certainty only by histological examination of biopsied tissue.

The Effect of [3,3'-Methylene-Bis-(4-Hydroxycoumarin)] (Dicumarol) on the Prothrombin and Coagulation Times of the Blood

Preliminary Report

F. A. LeFEVRE, M. D.

After experimenting with spoiled sweet clover for several years, Link and his associates¹ in 1941 isolated the active hemorrhagic factor (3,3'-methylene-bis-(4-hydroxycoumarin)] and were able to produce it by synthesis. This work was probably stimulated by the observations of Schofield² and Roderick.³ Although it had been known for many years that cattle occasionally showed signs of hemorrhage for no obvious reason, it remained for these workers to demonstrate that this hemorrhagic tendency was related to the eating of spoiled sweet clover. In June 1941 Butt, Allen, and Bollman⁴ reported that the oral administration of this compound to animals and man prolonged the prothrombin and coagulation times with an effect similar to that of heparin.

During the past six months this drug has been used clinically in over 20 cases in which such a reaction would be helpful in the management of the patient. Table 1 shows the clinical conditions treated.

Disease	No. of Cases
Pulmonary embolism postoperative.....	4
Acute thrombophlebitis.....	8
Rheumatic heart disease with subacute bacterial endocarditis.....	6
Thrombo-angiitis obliterans.....	4
Thrombosis retinal vein.....	1
Total cases.....	23

The following three cases are presented to show the effects of [3,3'-methylene-bis-(4-hydroxycoumarin)] on the prothrombin and coagulation times.*

Although no name has been definitely adopted for this preparation, it will be referred to as dicumarol in the following cases. These are among the earlier cases treated with this drug, and as yet the dosage has not been standardized. As will be observed, the drug was used in varying

*The Quick method is used for coagulation time, and Lee and White method for prothrombin time.

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amounts without regard to body weight. However, the reactions have been helpful in determining a more reliable form of dosage which at the present time is calculated chiefly on body weight.

Case 1. A man, aged 29, was admitted to the Clinic April 17, 1942 complaining that pain, weakness, chills and fever had been present for two months. Physical examination revealed that this patient was suffering from rheumatic heart disease, mitral stenosis, and insufficiency. Blood culture at the time of admission was positive for streptococcus viridans. A final diagnosis of subacute bacterial endocarditis was made.

My experience with various forms of treatment for this condition has been unsatisfactory, although the usual forms of chemotherapy have been applied for some time.

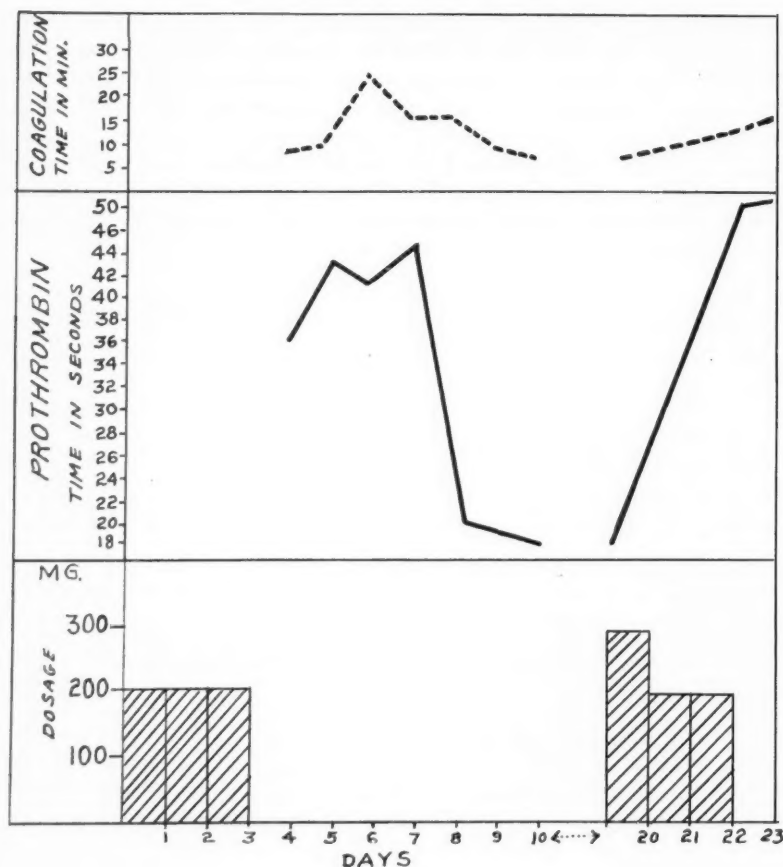


CHART 1

PROTHROMBIN AND COAGULATION TIMES OF BLOOD

Heparin also has been used in combination with some of the sulfonamide preparations. Because much of the effect of dicumarol is similar to that of heparin, it seemed logical to apply this preparation along with some of the sulfonamide drugs. For this patient sulfadiazine was combined with dicumarol. The patient was hospitalized, and on the first three days of hospitalization he was given 200 mg. of dicumarol daily. Chart 1 indicates the effect of this drug on the prothrombin and coagulation times. At the end of the third day there was a definite rise in the prothrombin time, the normal being 15 seconds. Medication was withdrawn on the third day, and at the end of the tenth day the prothrombin time had returned to normal. The coagulation time reached a peak of 25 minutes corresponding to the peak of the prothrombin time. The patient was dis-

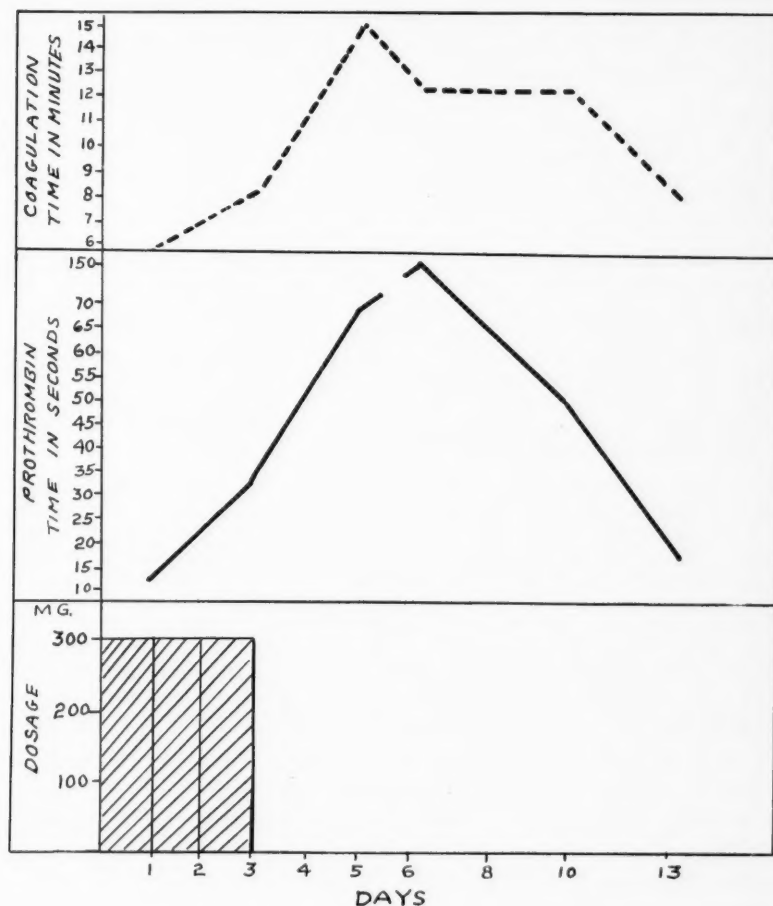


CHART 2

FAY A. LEFEVRE

charged from the hospital on sulfadiazine therapy which he continued at home. When he was readmitted to the hospital ten days later, the prothrombin and coagulation times were normal, and he was given a second dose as indicated on the chart. There was an immediate response which again lasted for ten days. This patient was followed for a period of several months following the initial use of the drug. The dosage was repeated on several occasions at intervals of about 14 days, and the reaction seemed to be fairly constant in each instance.

Although adequate levels of sulfadiazine were maintained, the patient continued to become steadily worse and died two months after starting treatment. During the course of treatment it seemed that the number of embolic reactions was reduced, although he continued to have them from time to time.

Case 2. A woman, aged 32, weighing 100 pounds was admitted to the Clinic May 5, 1942. Her complaints were referable entirely to the extremities. Examination indicated marked reduction in the peripheral circulation, and ulceration in several areas of the toes and fingers. After careful vascular studies a diagnosis of thromboangiitis obliterans was made. It is the first case in a woman that I have observed. The patient was hospitalized and various forms of treatment started in an attempt to improve the peripheral circulation. Because of the nature of the disease it was felt that any agent which might increase the prothrombin and coagulation times might be of help in the management of this type of patient.

Chart 2 indicates the patient's response. A total of 900 mg. of dicumarol was given over a period of three days. On the seventh day the prothrombin level rose to 150 seconds. At the same time there was a slight drop in the coagulation time to 12 minutes, the highest peak being 15 minutes. At no time during the course of treatment was there any evidence of hemorrhage. As far as could be determined, she suffered no ill effects from a rather marked change in the prothrombin time. The coagulation and prothrombin times returned to normal in approximately 13 days. Inasmuch as other forms of treatment were employed at the same time, it was impossible to tell whether or not this patient received any benefit from this type of preparation.

Case 3. A man, aged 42, weighing 175 pounds was admitted to the Cleveland Clinic Hospital April 8, 1942 with an extensive acute thrombophlebitis. The etiology was not determined. There was no involvement of the peripheral arterial system. Previously, heparin has been used in this type of case, and, accordingly, dicumarol seemed to be the ideal drug. Chart 3 represents the patient's reaction. He was given 200 mg. of dicumarol on the first day and 100 mg. on the second and third days. A prompt response was noted in both the prothrombin and coagulation times, and at the end of ten days, there was still some elevation. The patient made a rather rapid clinical recovery and has been observed regularly since his discharge from the hospital. Again it was impossible to determine the effects of this drug on the course of the disease as the patient was in bed. Frequently, the symptoms respond promptly to bed-rest alone.

COMMENT

The chief purpose of this report has been to show the effect of dicumarol on the prothrombin and coagulation times. Although several clinical conditions have been treated with this drug, it is impossible to state at the present time whether or not any benefit has been derived from its use. Observations would indicate that the drug is effective in

PROTHROMBIN AND COAGULATION TIMES OF BLOOD

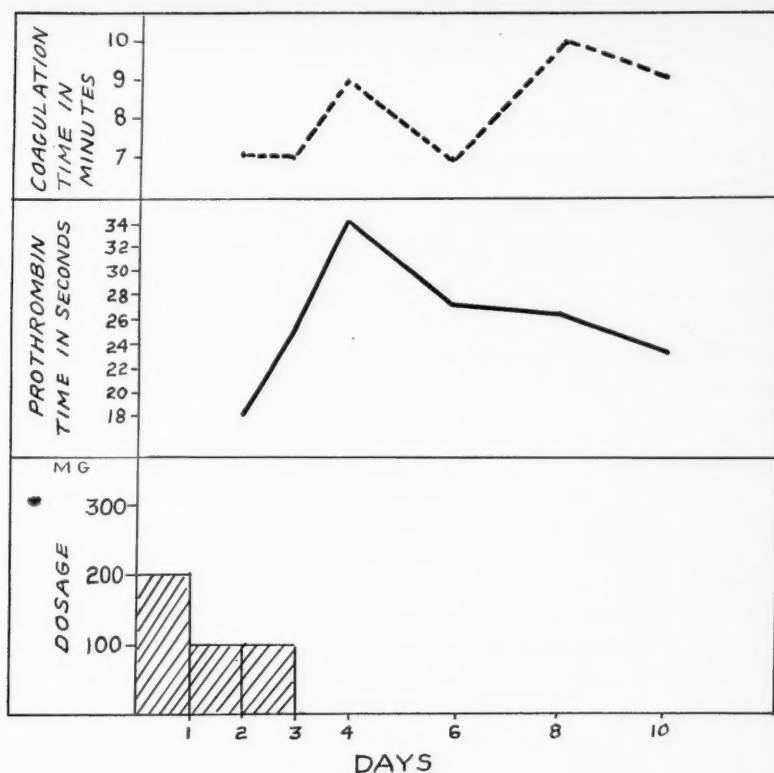


CHART 3

increasing the prothrombin and coagulation times. As a general rule, there is a delay in the rise of about 24 to 48 hours. At the end of this time with proper dosage there should be a prompt rise in both levels which is maintained for 10 to 12 days. The drug may be administered again at the end of this time with a prompt rise in the levels. Although no standard dosage has been worked out, an initial oral dose of 5 mg. per kilo. seems to be effective. A subsequent equal dose on the two following days can be given with safety and produces an adequate rise in both the prothrombin and coagulation times. Recently, I have been inclined to reduce the dose on the third day to $2\frac{1}{2}$ mg. per kilo.

Because of the rather marked fluctuations that are obtained by the present method of administering the drug, an attempt has been made to

establish a small daily maintenance dose. This seems to be the ideal way to administer the drug, and no doubt in the near future the proper dosage by weight will be determined. Dicumarol also has been given intravenously, but I have had no personal experience with this method of administration.

It does not seem necessary to raise the prothrombin levels as high as in the cases presented in this report, although no untoward effects have been observed during this study. The effect of dicumarol on the hemoglobin level, red blood cell count, and white blood cell count was observed, and at no time were any abnormalities found. Lower levels of prothrombin and coagulation times are desirable until further experience and more confidence in the safety of the drug has been established. There is no direct relationship between the rise in prothrombin and coagulation times.

SUMMARY

A small series of cases has been treated with dicumarol, and the reactions are reported. Dicumarol has a definite effect upon the prothrombin and coagulation times. As yet its therapeutic value has not been established.

We are indebted to Dr. F. B. Peck of Eli Lilly and Co. for furnishing us with the material and indication to dosage.

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STUDIES ON THE EFFECTIVENESS OF INSULIN IMPLANTS

E. PERRY McCULLAGH, M.D. and LENA A. LEWIS, Ph.D.

Ever since an active preparation of insulin was secured, methods have been sought for administering the hormone by some means other than injection. Major¹ reviewed the results which had been reported up to 1936. Since then numerous reports have been published, of which the following summarizes the more pertinent findings.

Parkes and Young² in experiments on rabbits found that the hypoglycemic action of amorphous insulin pellets was only slightly more prolonged than that of a similar amount of insulin in solution administered subcutaneously. Crystalline insulin pellets had a similar duration of action despite the fact that the tissue capsule around the pellet contained appreciable amounts of insulin.

Using depancreatized dogs Mark et al³ found that pellets of crystalline zinc insulin with protamine were effective for as long as 100 hours. The pellets on examination four hours after implantation were swollen, and there was edema at the site of implantation.

Cutting et al⁴ reported briefly on the effective use of pellets of cholesterol and insulin in depancreatized dogs. They observed a slow release of insulin during periods as long as 13 days. The irregularities of absorption were too great to justify the trial of such pellets in the clinical treatment of diabetes.

EXPERIMENTAL

Methods. Adult dogs maintained on a constant diet were used. They were fed at 3 p. m. daily. Blood was drawn from the saphenous vein when the dog was in the postabsorptive state. All excitement was carefully avoided. Blood sugar was determined by the Somogyi modification of the micro-Shaffer-Hartman method.⁵ Blood sugars were taken on the untreated animal at two-hour intervals. At the same times on other days they were taken following subcutaneous administration of amorphous insulin to determine the animal's response to various amounts of this hormone. Protamine zinc insulin was also tested. Preliminary experiments showed that cylinders packed with albumen with a molecular weight approximating that of insulin would deliver roughly 1.0 mg. per day to solution if the inner diameter of the cylinder was 2.0 mm.

and it was open at each end. Tubes of this size and 100 mm. in length were then packed with 25 to 30 mg. crystalline insulin and implanted subcutaneously.

Pellets weighing 325 mg. with a surface area of 2.5 sq. cm. and composed of a mixture of insulin and cholesterol were prepared. Twenty per cent insulin and 80 per cent cholesterol proved most satisfactory. They were sterilized by heating at 100° C. for one hour on three successive days. The capsules and pellets were implanted subcutaneously using local anesthesia.

Results. Following subcutaneous implantation of the silver capsules filled with insulin the blood sugar levels fell to approximately those observed following 20 to 30 units of protamine insulin. Chart 1 summarizes the results obtained on Dog N. After three to four weeks when the capsules were removed they were found to contain appreciable amounts of potent insulin. Examination of the tissue surrounding the capsule showed a mass of granulation and young fibrous tissue typical

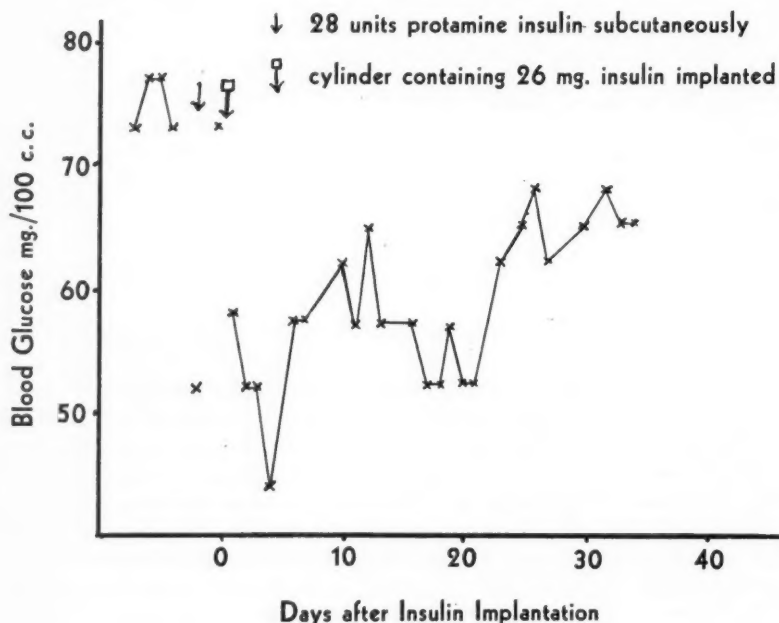


CHART 1

EFFECTIVENESS OF INSULIN IMPLANTS

of that forming around a nonirritating foreign body. It appears that the release of insulin is greatly impeded by this tissue.

The implantation of the insulin-cholesterol pellets was also followed by a marked drop in blood glucose. Chart 2 summarizes the results on Dog S. In some cases a second pellet was implanted about one month after the first one. In each case the response was similar to that following the first implantation which showed that the animal was still sensitive to insulin. After several weeks when the pellets were removed they were surrounded by a capsule of tissue which presented a picture on histological examination similar to that surrounding the silver capsule-insulin implant. The pellet inside the tissue capsule had become "mushy," and it appeared to be maintained in shape by the tissue surrounding it. The entire pellet was moist. The material, however, still had marked insulin potency. Further studies are being carried out on relative effectiveness of different paths for the administration of insulin.

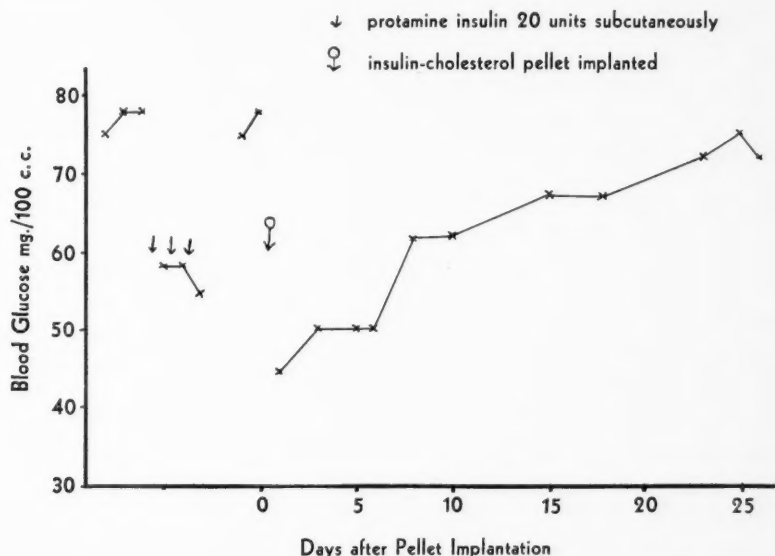


CHART 2

SUMMARY

The subcutaneous implantation into the dog of silver capsules firmly packed with crystalline insulin is followed by a definite drop in the blood sugar level. The insulin effect gradually decreased until no appre-

ciable change in blood sugar level was observed after two to three weeks despite the fact that appreciable amounts of potent insulin were still in the capsule. Similar results were obtained following the subcutaneous implantation of pellets of insulin and cholesterol.

We are indebted to Eli Lilly and Co. for the crystalline insulin used in these experiments.

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